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09/913,967	12/31/2001	Wilhelmus Evergardu Hennink	313632001000	8024

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/913,967	HENNINK ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 21-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The last office action is vacated in view of applicant's request for reconsideration.

Examiner acknowledges receipt of request for extension of time, IDS, amendment and remarks, all filed 11/17/06. Claim 1 is amended. Claims 1-17 and 21-26 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 1-14 and 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

Nature of the Invention: The scope of the invention encompasses a water-soluble or water dispersible hydrophilic polymer in an aqueous system that is substituted with oligomers or co-oligomers. However, the specification as filed has not conveyed with reasonable clarity how the substitution of the oligomer for the polymer is carried or what portion of the polymer is being substituted for by the oligomer and what the substituted polymer is or how it looks like. The

specification in the examples describes grafting lactides, L- and D- forms onto dextran by the series or polymerization/oligomerization reactions described in the specification (Examples 1, 2, 4). These reactions are not substitution reactions and the specification does not show equivalence of substitution with grafting so that the specification has not provided possession of water-soluble or water dispersible hydrophilic polymer that is substituted with an oligomer or co-oligomer --- the specification does not show or name water-soluble or water dispersible hydrophilic polymer substituted with an oligomer or co-oligomer. The specification does not name the product formed by claim 21 and the specification does not posses the product formed by the claim 21 where no clear choice of water-soluble polymer is prescribed. There is no description in the specification for what a "releasable compound" is and thus does not possess releasable compound as claimed in claim 21.

4. Claims 1-5, 7-17 and 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dextran polymer onto which is grafted lactide, does not reasonably provide enablement for all polymers and all oligomers and co-oligomers, and all bifunctional oligomers and all bifunctional oligomers that form parallel stereocomplexes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is scope of enablement.

The Nature of the Invention: The invention is directed to all water-soluble or water dispersible polymers that are substituted with any and all oligomers or co-oligomers.

The Breadth of the claims: The scope of the claims is open to any water-soluble or water dispersible polymers and any and all oligomers or co-oligomers. The scope of the claims is not

commensurate with the enabling disclosure where L- and D-lactide oligomers are grafted onto dextran, a water-soluble polymer.

The state of the prior art: The prior art is what the prior art knows. Ethyl cellulose is known in the art as a water insoluble polymer, while hydroxyethyl cellulose, methylcellulose and polyvinylpyrrolidone are water-soluble polymers and several more. In similar manner, there are other oligomers such as bifunctional styrene oligomer, which is not one of those listed in the specification and recited in dependent claim 2.

The quantity of Experimentation Needed: Guidance is provided only for dextran and lactide, and this guidance is not commensurate with the full scope of all polymers and oligomers claimed. While the specification further lists a number of polymers and oligomers on pages 11 and 12 at lines 21-36 and 1-10 respectively, the list is by no means commensurate with the scope of all oligomers and polymers claimed. Applicant on page 7 of the remarks filed 11/17/06, at the last two lines of the first full paragraph, states that it is known in the art that all optically active polyesters do not form stereocomplexes. There is thus an element of unpredictability in at least oligomers and their ability to form stereocomplexes. Thus, the listing of the oligomers represent an invitation to fishing expedition to determine which of the oligomers can form stereocomplexes and be grafted on to any polymer.

Therefore, the quantity of experimentation needed to practice the full scope of the claimed invention is undue and the full scope of the claimed invention has not been enabled by the specification.

Applicant may overcome this rejection by reciting in at least claims 1, 5, and 15 the enabled dextran polymer and oligomer derived from lactide.

5. Claims 1-14, 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that a water-soluble or water dispersible hydrophilic polymer is substituted with oligomers or co-oligomers. It is unclear what applicant means by substituting the water-soluble or water dispersible hydrophilic polymer with oligomers. In order to expedite prosecution, claim 1 and does dependent therefrom are examined as polymers substituted by oligomers.

Claim 3: The meets and bounds of "substantial part of said groups of mixture A" are not defined and is thus unclear what the meets and bounds are. The meets and bounds of "moiety" are not defined and is thus unclear what the meets and bounds are.

Claim 4: It is unclear which moiety has hydroxyl and which moiety has a carboxylic acid.

Claim 6: The meets and bounds of "cellulose derivatives," "related copolymers" of poly(lysine) and poly(glutamic acid) are not defined in the claims.

Claims 8-10: It is unclear and is not defined what amounts or values of chain length of the oligomer or degree of substitution that is sufficient to render the polymer soluble or dispersible in water.

Claim 14: This claim is confusing because it is not clear in the claim that the oligomer is grafted onto any polymer ore any structure.

Claim 25: It is unclear how administration of a drug delivery device is by *in vitro* as recited in claim 25.

Claim 24 delivers a drug by administering the composition of claim 1 that does not contain any drug. It is confusing how a drug can be delivered from a delivery device that does not contain any drugs.

Claim 9: It is unclear what the water-soluble or water dispersible polymer is physically interacting with.

Claim 21: The scope of releasable compound is not discernible. The meets and bound of releasable compound is not known.

6. Claims 1 and 3 recite the limitation "said groups" in lines 10 and 2 respectively. There is insufficient antecedent basis for this limitation in the claim in claim 1.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-5, 7-10 and 13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Okihara et al. (J. Macromol. Sci. Phys. (1991) B30 (1 & 2) 119-140, submitted on form PTO-1449).

Okihara discloses a stereocomplex mixture poly(L-lactide) and poly(D-lactide) and the mixture comprises equimolar amounts of the L- and D-lactide forms (abstract and page 120, paragraph 1). The mixture inherently forms hydrogel. Regarding instant claims 3-5, 8-10 and 13,

the stereocomplex of Okihara would inherently have the instant property since the property of a composition cannot be separated from the composition. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705,709, 1 5 USPQ2d 1655, 1658 fled. Cir. 1990).

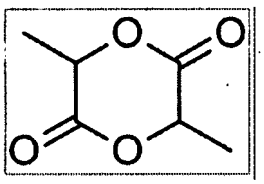
Response to Arguments

9. Applicant's arguments filed 11/17/06 have been fully considered but they are not persuasive.

Applicant argues that a) the molecular length of the Okihara's complex would be from about 69 monomer units to over 4,100 monomer units; b) X-ray analysis of the crystalline stereocomplex showed a tightly packed complex than the poly (L-lactide) homopolymer; c) Okihara disclosed that not all optically active polyesters formed stereocomplexes; d) poly(lactide) polymers do not constitute water soluble or water dispersible polymers; e) Okihara discloses crystalline stereocomplex formed by crystalization form 0.04% acetonitrile in p-xylene with slow cooling to 54 °C; f) the stereocomplex is not substituted with oligomers or co-oligomers.

Response:

Regarding a) it is noted lactide is a di-ester of lactic acid and has the structure noted as



having formula weight of about 144, which as per applicant's estimation would translate the 5000 to about 35 units and not the 69 units according to applicant's remarks; nonetheless, oligomers can have monomer units of between 10 and 100 as evidenced by Craun et

al. (US 7,049,357) at column 4, lines 40 and 41 where it is said that PLA oligomer having molecular weight of 2000 to 6000 is synthesized, with the 6000 translating into about 42 units. Regarding b) and e), examiner agrees with applicant that the X-ray data is obtained from crystalline stereocomplex of lactide and glycolide. However, it is noted that the lactide/glycolide complex was formed or existed before crystallization of the product. Regarding c), the claims are not directed to any specific polyesters that form or do not form stereocomplexes. Regarding d), it is noted that the claims require substitution of the polymer with the oligomers so that the product is the oligomer. Regarding f), it is noted that when the polymer is substituted with oligomers, the resulting product is the oligomer.

10. Claims 1-10, 14 and 21-26 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hennink et al. (WO 98/00170, cited on form PTO-1449).

Hennink discloses a biodegradable hydrogel that contains hydrolysable bonds and where the hydrogel consists of two interpenetrating polymer networks interconnecting to one another through hydrolysable spacers (abstract). In Hennink, (poly)glycolic acid and/or (poly)lactic acid spacers are introduced between polymerizable methacrylate groups and dextran (page 7, lines 24-27 and page 8). The hydrogel is prepared by a radical polymerization in the presence of tertiary amine and persulfate initiator (page 9, lines 14-23). Increasing degree of substitution (DS) yields a more cross-linked network (page 9, lines 31-34). Drugs are loaded onto the hydrogel during polymerization or cross-linking (page 10, lines 24 and 25). The hydrogel of Hennink are applied as microspheres of varying sizes (page 10, lines 26-34). See also examples 1-5 for preparation of hydrogels. The teachings of Hennink meet the limitations of the claims.

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 1 5 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Response to Arguments

11. Applicants' arguments filed 11/17/06 have been fully considered but they are not persuasive.

Applicant argues that Hennink does not disclose two polymers that are substituted with chiral oligomers; applicant's first and second points in the argument are the same with each sating that the prior art of Hennink does not disclose two polymer strands.

Response:

Regarding the absence of specific chirality in Hennink, it is noted that the prior art meets the limitation of the oligomers recited in claim 2, which defines the oligomers of claim 1: A racemic molecule has equal components of each component of the opposite chirality. Regarding specific claimed chirality, it is noted that the composition claims do not exclude or include covalent or non-covalent interaction. Furthermore, the composition is a blend of A and B, where the hydrophilic polymer in A is not different from that in B, so that within the blend is present a racemic the hydrophilic polymer and the oligomers of lactic or glycolic acids. Further still, Hennink discloses that the composition comprises two interpenetrating polymer networks (claims 2). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, Hennink anticipates claim 1 and claims 2-10, 14 and 21-26.

12. Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Hakomori et al. (US 5,230,900).

Claim 23 is a product by process claim. The product is a microsphere.

Hakomori discloses a microsphere composition that includes lactide glycolide copolymers, polyacrolein graft copolymer, carboxymethyl dextran, or polylactide and polystyrene or combinations (column 3, lines 50-56). Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." MPEP 2113 [R-1].

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennink et al. (WO 98/00170, cited on form PTO-1449).

Hennink clearly teaches the instant hydrogel composition. Hennink teaches that increasing degree of substitution (DS) yields a more cross-linked network (page 9, lines 31-34). As it regards claim 12, Hennink discloses that the hydrophilic polymer contains polylactic or polyglycolic acid and Hennink specifically describes the presence of one or more units of the lactic or glycolic acid (page 9, line 12) so that lactic acid or glycolic acid used in Hennink would have one or more units of the acid that would provide the desired release of the incorporated active upon hydrolysis/degradation of the lactic or glycolic. Regarding claim 13, Hennink is silent on the length of the oligomeric groups and it flows that a racemic mixture of lactic acid or glycolic acid would have equal lengths such that in the combination is racemic. Hennink does not teach a degree of substitution of 3-25 as recited in instant claim 11. There is no comparable example to demonstrate that a degree of substitution of 3-25 provides unusual results. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a stereocomplex hydrogel that has appropriate degree of substitution since according to the teaching of Hennink degree of substitution is related to how cross-linked the polymer network is. One having ordinary skill in the art would have been motivated to prepare

a stereocomplex hydrogel composition with a varying degree of substitution with the expectation of obtaining a hydrogel with the desired cross-linked network.

16. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Jong et al. (Macromolecules, 1998, 31:6397-6402, provided by applicants on form PTO-1449) in view of Brannon-Peppas (Int. J. Pharm., 1995, 116:1-9, provided by applicants on form PTO-1449).

De Jong discloses preparation of stereocomplexes homo- or copolymers of D- and L-lactides and further discloses that stereocomplex formation is also observed in blends of L-lactide/ε-caprolactone and D-lactide/ε-caprolactone (abstract and page 6397). Synthesis of the stereocomplex begins with preparing the oligomer in the presence (2-tmethoxyethoxylethanol (MEE)) initiator and stannous octoate catalyst (page 6399).

De Jong does not teach incorporating active ingredient in the stereocomplex. However, Brannon-Peppas discloses that copolymers of polylactic acid are drug carriers (abstract). Regarding the sequence or preparing the drug containing hydrogel, selection of any order of the preparation steps in instant claims 15-17 is obvious in the absence of unexpected results showing that the order recited in the claims provides unusual results. Therefore, it would have been obvious to one of ordinary skill in the at the time the invention was made to include an active ingredient in the hydrogel composition of De Jong since Brannon-Peppas teaches that lactide hydrogels can be drug carriers. One having ordinary skill in the art would have been motivated to include active agents in the lactide hydrogel formulation of De Jong with the expectation that the stereocomplex lactide hydrogel would serve as a carrier.

Response to Arguments

17. Applicants' arguments filed 11/17/06 have been fully considered but they are not persuasive.

Applicant argues that

a) Hennink cannot render claims 11-13 obvious because, Hennink does not suggest polymers that are substituted with complementary chiral groups that interact noncovalently.

Response:

The response given above for Hennink shows that a racemic mixture contains equal amounts of the L and D-forms of the acids and therefore, Hennink anticipates the claims and renders obvious the claims as described above. Claims 11 and 12 are directed to mixtures of lactic acid polymers.

b) that De Jong employs poly disperse lactic acid oligomers prepared by using 2-(2-methoxyethoxy)ethanol as initiator and stannous octoate as catalyst; that the stereocomplexes of De Jong are not hydrogels according to Professor Hennink's declaration; that there is no motivation to combine Brannon-Peppas with De Jong because Brannon-Peppas does not overcome the deficiency of De Jong and neither of the two references disclose two water soluble or water dispersible hydrophilic polymers.

Response:

The initiator 2-(2-methoxyethoxy)ethanol and catalyst stannous octoate meet the generic recitation of suitable initiator. Claim 13 does not exclude using 2-(2-methoxyethoxy)ethanol as initiator and stannous octoate as catalyst since no specific initiator and catalyst are recited in the

claims. Claim 13 is the process of preparing a hydrogel by polymerizing a monomer and in this case De Jong discloses lactide monomers (see applicant's specification at page 41, lines 22-25). Since De Jong uses the same components in its process as for the claimed process, it flows that the product formed from the same starting materials using same initiators would yield hydrogel. Therefore, Brannon-Peppas does not have to overcome hydrogel deficiency because the product formed by the process of De Jong is inherently a hydrogel. The motivation to combine Brannon-Peppas with De-Jong is found in Brannon-Peppas disclosure that copolymers of polylactic acid are used as drug carriers and Brannon-Peppas makes up for the deficiency that De-Jong does not have drug incorporated in the hydrogel product.

The declaration by Professor Hennink was previously addressed and noted that the declaration is not commensurate with the invention in terms of formation of hydrogel **only** in water because applicant's Example 1, for example, is prepared in organic solvent and applicant's examples 1, 2 and 4 appear to contradict Exhibit 3 submitted with the declaration.

Claim Objections

18. Claim 22 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

In current claim 22, the hydrogel is according to claim 1 and there is a further requirement that the claim derive form any one of the preceding claims. This is improper according to the stipulations of MPEP § 608.01(n).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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